Our wonderful immune system

- Our immune system has protected us from all infectious organisms so far encountered and saved us from extinction.

- Two things have been central to our survival:
  - the ability to develop natural immunity to the pathogen in question and
  - the declining virulence of the pathogen itself.

Immune system lines of defence

- The immune system defends against infectious organisms (viruses; bacteria; parasitic worms; fungi), as well as cancer cells, toxic chemicals and objects such as wood splinters.
- **First line of defence** against pathogens is our **barriers**: skin and mucous membranes of the digestive, respiratory and reproductive tracts. The skin covers around 2 square meters, while mucous membranes cover around 400 square meters (2 tennis courts).
- **Second line of defence** is the **innate immune system**, which carries out immune surveillance for pathogens that have breached the physical barriers and eliminates them using circulating macrophages, inflammatory cytokines and natural killer (NK) cells. It also activates the adaptive immune system if necessary.
- The innate immune system cells move to the affected area and release chemicals that make the blood vessels wider and more permeable. This causes the area around the infection or injury to swell, heat up and redden and inflammation and possible fever results. The innate immune system functions by communication and cooperation; it is fast-acting but inflexible and non-specific.
- However, the innate immune system is not very effective against viruses. This is when we need….

Immune system lines of defence: the adaptive immune system

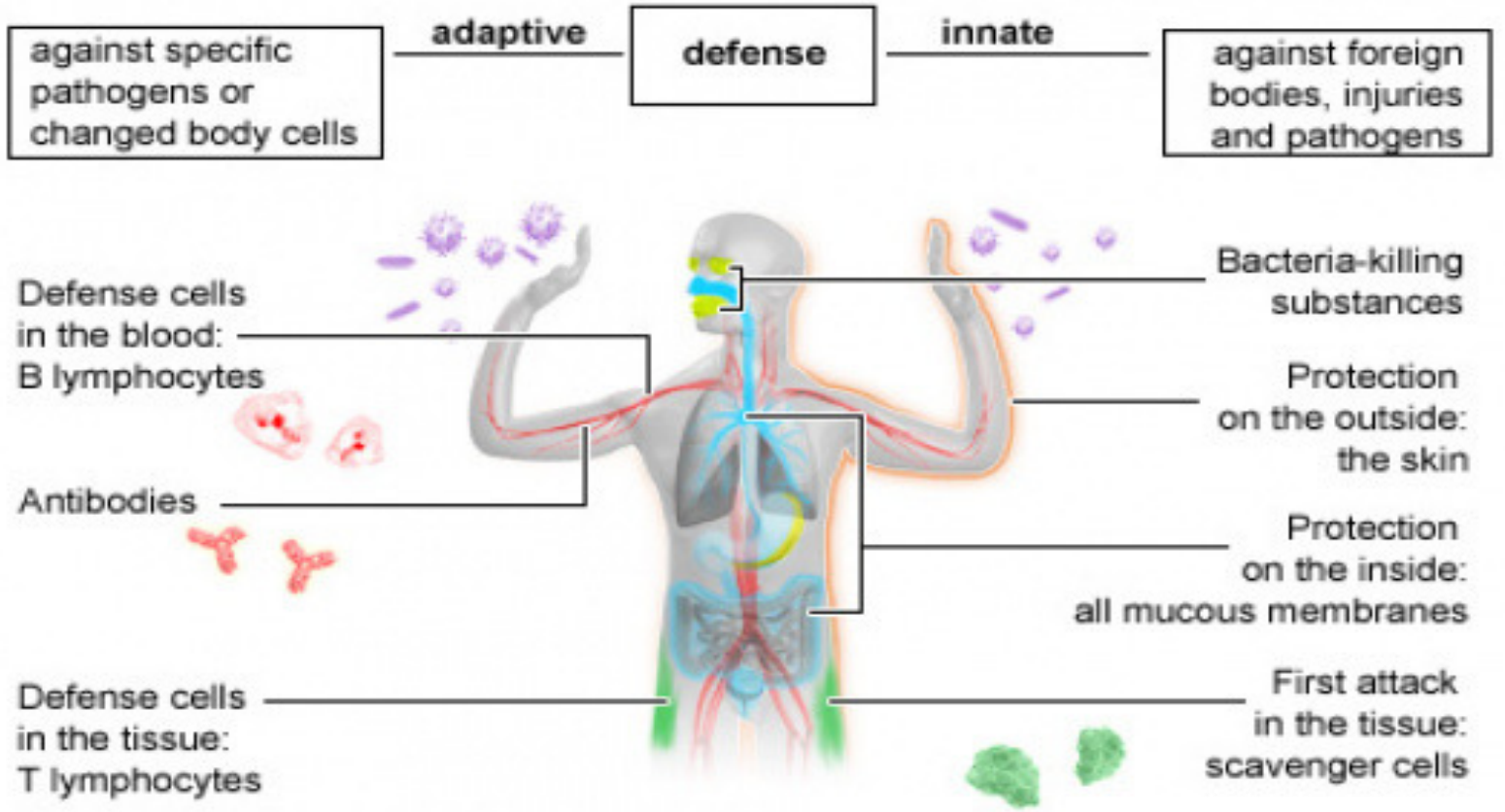
- **Third line of defence** is the adaptive immune system, which provides a tailored response to each pathogen.
- This makes it considerably slower (likely, several days) than the innate immune system (immediate) as it cannot mount a response until the microbe has been identified. It is, however, considerably more specific and accurate in destroying the microbe before it takes hold in the body.
- The adaptive immune system is made up of:
  - B lymphocytes, which make antibodies,
  - T lymphocytes (T cells)
- The adaptive immune system also generates an immunological memory in the form of antibodies, memory B cells, memory T cells and memory NK cells to every pathogen encountered by the innate immune system.
- Both the innate and adaptive immune system also have to distinguish these infectious organisms etc from our own healthy tissue to avoid autoimmune conditions. The distinction between self and non-self is critical. If under-active, then pathogens may be allowed free access to the body; if over-active, autoimmune conditions can develop.

Understanding the innate and adaptive immune systems

Innate immune system: a bobby on the beat

Adaptive immune system: specialist detectives assigned to drug squad, vice, etc

Components of the immune system



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Components of the innate immune system

- Phagocytes (white blood cells, or leukocytes). See following slide.
- Cytokines and chemokines. See following slide.
- Dendritic cells, which specialise in pathogen recognition but can also have phagocytic properties and secrete cytokines. They connect the innate and adaptive arms of the immune system and can function as antigen presenting cells (APCs) in the adaptive immune system. They control inflammatory responses, promote tolerance and recruit immune cells.
- The complement system, a cascade of up to 30 proteins working together, marks pathogens for destruction (they are known as the 'poor man's antibodies'), enhance their destruction and signal to other components of the immune system. They can also puncture the envelope of enveloped viruses. The principal complement protein is C3.
- Innate lymphoid cells (ILCs), which reside in the mucosal epithelia. The best known are natural killer (NK) cells, which secrete signalling molecules and regulate both the innate and adaptive immune cells. NK cells are lymphocytes which specialise in identifying cells infected by a virus as they have surface alteration. Once identified, they destroy the cell (degranulation), using their enzymes perforin and granzymes, can trigger a cell to commit apoptosis and can also rapidly produce interferon-gamma (IFNγ). NK cells form part of both the innate and adaptive immune systems.
- Enzymes, which mark microbes as targets and attract other immune system cells from the bloodstream. They attack viruses by destroying the viral envelope or cells that have been infected with viruses. Pus, a yellowish fluid, is the remains of dead and decayed microbes, enzymes and immune cells.
- Mast cells mediate the acute inflammatory response at sites of trauma or infection, acting similarly to dendritic cells. They release histamine, leukotrienes and other molecules to increase vascular permeability to aid blood supply.
- Cytotoxic T lymphocytes: shared between the innate and adaptive immune systems. Within the innate immune system, these cells are able to kill the virus before it enters a cell.

Phagocytes

Phagocytes (from ‘phagein’, Greek for ‘to eat’) are white blood cells (leukocytes). They locate the microbes aided by complement or antibodies and enclose and digest them. They include:

- Macrophages (‘big eaters’) engulf a pathogen to form a vesicle (phagosome) which fuses with a lysosome (vesicles containing lytic (destructive) chemicals) to destroy it (phagocytosis) through deployment of the lysosome’s enzymes and other chemicals.
- At the same time, macrophages produce and secrete cytokines (see following slide). In this function, macrophages may be pro-inflammatory (M1 macrophages) or anti-inflammatory (M2 macrophages).
- In addition, the macrophage deposits some of the micro-organism debris, which alerts other components of the innate immune system that an intruder has been located. This initiates an inflammatory response (reinforcements for the macrophages).
- Macrophages can also inhibit initial viral replication by triggering interferon type 1 (IFN-I) activity.
- Monocytes (macrophage precursors circulating in the blood),
- Smaller polymorphonuclear leukocytes (PMNs), including neutrophils, eosinophils and basophils. Neutrophils are short-lived killer cells, the immune system’s primary defence against infection, producing the pus seen in infections. They can form Neutrophil Extracellular Traps (NETs), which are networks of extracellular fibres, primarily composed of neutrophil DNA, which bind pathogens.

Cytokines

- Cytokines are peptides, comprising chemokines, interferons (see next slide), interleukins and tumour necrosis factors. They are produced by a broad range of immune cells, including macrophages, B lymphocytes, T lymphocytes and mast cells, as well as other cell types.
- Cytokines are important in health and disease, specifically in host immune responses to infection, inflammation, trauma, sepsis and cancer. They often act as the first responders to a pathogen infection.
- The main function of cytokines is cell signalling. They act as chemical messengers through cell surface receptors and are especially important in the immune system, modulating the balance between humoral and cell-based immune responses (B cells/antibodies and T cells). They stimulate the adaptive immune response and recruit other immune cells to the site of infection.
- Cytokines are typically not stored within the cell but instead are synthesised on demand, often in response to another cytokine. Once secreted, the cytokine binds to its receptor on the surface of the target cell, an event that triggers a signaling cascade inside that cell. The signal ultimately reaches the nucleus, where the effects of the cytokine are manifested in changes in gene transcription and protein expression.
- Cytokines can either promote inflammation or suppress it. However, a ‘cytokine storm’ aka cytokine release syndrome, may develop, defined as an uncontrolled and excessive release of pro-inflammatory cytokines. Immune cells then spread beyond infected body parts and start attacking healthy tissues, especially blood vessels, giving rise to blood clots. Indicators of a cytokine storm include excessively high levels of serum pro-inflammatory cytokines (particularly IL-6), ferritin and C reactive protein (CRP). There is disagreement about how the cytokine storm differs from an appropriate inflammatory response.

Interferons (IFNs)

- Interferons are components of both the innate and adaptive immune system and are derived mainly from dendrocytes. They are principally involved in anti-viral activity, modulating the innate immune response and activating the adaptive immune response. IFNs are activated by ubiquitination (the addition of ubiquitin to a substrate protein).
- Types of interferon:
  - Type I interferon consists of INF-α, INF-β and INF-ω and is expressed in response to viral infection.
  - Type II interferon consists only of INF-γ and is associated with activating macrophages to control intracellular pathogens and tumour suppressor genes.
  - Type III interferon consists of INF-λ and is associated with viral immune response and is key in anti-fungal neutrophil response.
- Upon infection, transient high production of IFNs induces the expression of interferon-stimulated genes (ISGs). Some fortify cells' outer defences to prevent viral entry, some boost the internal defences of infected cells, while others stop newborn viruses from leaving an infected cell. Interferons also engage receptors on various immune cells, recruiting them to the body's battle with the virus. Type 1 IFN can trigger expression of 450 genes associated with suppression of viral replication and increased expression of immune signalling proteins.
- IFN-I is a strong immune modulator with a wide range of antiviral functions: induction of expression of antiviral proteins, restriction of viral protein synthesis, induction of apoptosis of infected cells, promotion of the maturation and activation of dendritic cells, promotion of the activation of the adaptive immune response.
- Interferons prevent replication of viruses by directly interfering with their ability to replicate within an infected cell. They also act as signalling molecules that allow infected cells to warn nearby cells of a viral presence - this signal makes neighbouring cells increase the numbers of MHC class I molecules upon their surfaces, so that T cells surveying the area can identify and eliminate the viral infection as described above.
- IFNs have an anti-proliferative effect that can inhibit the division of tumour cells and also upregulate natural killer (NK) cell release, which can destroy viruses and eliminate tumour cells.
- IFNs have been used therapeutically but can have adverse effects.

- Li JY, et al. Innate Immunity Evasion Strategies of Highly Pathogenic Coronaviruses: SARS-CoV, MERS-CoV, and SARS-CoV-2. Front Microbiol. 2021 Oct 29;12:770656
- IFN-I is a strong immune modulator. It has a wide range of antiviral functions: (1) it can induce the expression of various antiviral proteins and restrict the synthesis of viral proteins, thus impairing virus replication; (2) it can induce apoptosis of infected cells, eliminating the “virus production factory”; (3) it can promote the maturation and activation of dendritic cells, promoting the activation of the adaptive immune response.

Innate immune system: action of pattern recognition receptors (PRRs)

- To sense pathogen invasion, mammalian cells have evolved several pattern-recognition receptors (PRRs), including Toll-like receptors (TLRs), complement proteins, C-type lectin receptors (CLRs), nucleotide-binding oligomerization domain (NOD)-like receptors (NLRs), absent in melanoma (AIM) 2-like receptors (ALRs) and retinoic acid-inducible gene I (RIG-I)-like receptors (RLRs).
- These receptors recognise either pathogen-associated molecular patterns (PAMPs) or cellular damage caused by pathogens (damage-associated molecular patterns - DAMPs).
- Upon PRR activation, downstream signalling cascades trigger the secretion of inflammatory cytokines and chemokines; among these, type I/III interferons (IFNs) are considered the most important for antiviral defence. Together, they induce antiviral programmes in target cells and potentiate the adaptive immune response. PRR activation also induces apoptosis (intentional cell death) to clear out infected cells, as well as activation of the adaptive immune system.
- The inflammatory response includes assembly of inflammasomes (macromolecular complexes that trigger the maturation and release of proinflammatory cytokines of the innate immune system) as well as caspases that lead to cell death by pyroptosis.
- The inflammasome may serve as a biomarker to indicate the severity of disease.

Innate immune system: mechanisms of viral immune escape

- Entering a cell, where the innate immune system cannot operate.
- Secreting viral proteins that block toll-like receptor (TLR) and other signalling.
- Secreting viral proteins that block complement activation.
- Encoding a viral MHC Class I homologue, which tricks the natural killer (NK) cell into inactivity.
- Infecting and destroying NK cells, blocking production of cytokines and interfering with cytolytic action (especially HIV and Herpes Simplex virus).
- Infecting dendritic cells via a surface lectin (especially HIV).
- Molecular mimicry: encoding viral anti-inflammatory proteins (Epstein Barr virus) or molecules similar to the TNF receptor (pox viruses) or inhibiting IFN production. All of these neutralise innate immune system cytokines.

Innate immune system under- or over-activation

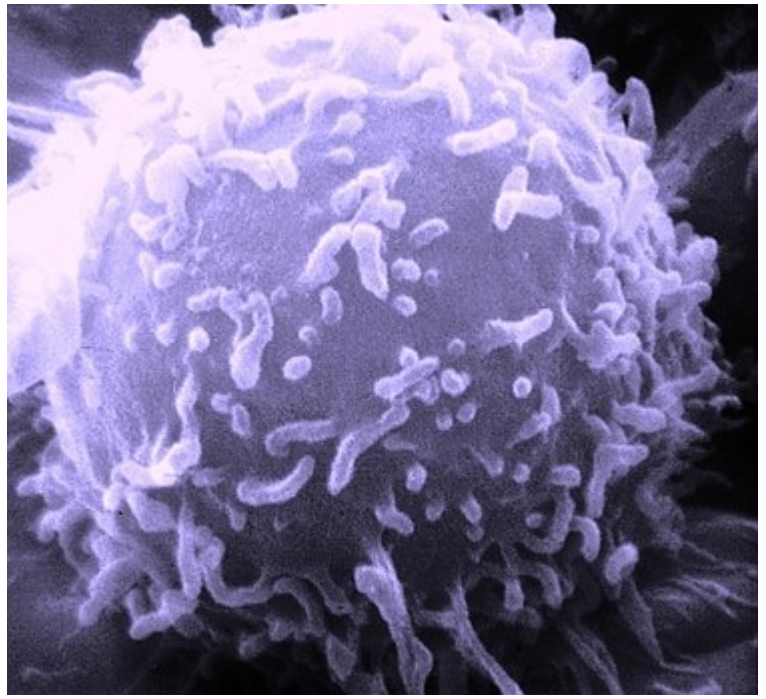
- If the innate immune system does not recognise an invading organism as a pathogen, it will not be activated and will, in turn, not activate the adaptive immune system.
- The immune system may also be under-active due to immunodeficiency, either due to congenital defects (e.g. causing cystic fibrosis) or damage in later life (often caused by malnutrition, inadequate levels of immune-supporting nutrients, increased susceptibility from prior infections such as HIV, radiation and chronic disease such as diabetes).
- However, immune system over-activation can also be pathogenic, inducing the cytokine storm and sepsis.
- Sepsis is the failure of one or more organs due to over-reaction to infection by phagocytes and the complement system. Complement over-activation can lead to inflammation and damage to small blood vessels, leading to leakage of fluid into the lung alveoli, seen in acute respiratory distress syndrome (ARDS). Widespread blood clotting, upregulated fibrinolysis, decreased oxygen supply and low blood pressure can lead to the often fatal septic shock.
- Excessive activation of NK T cells has been implicated in allergic asthma, while phagocytes and complement have the potential to damage healthy cells as well as pathogens.

The adaptive immune system

- The adaptive immune system adapts its response to protect us from almost any invading organism and is particularly helpful against viruses, where the innate immune system is not always sufficiently effective.
- The lymphocytes of the adaptive immune system are divided into two arms:
  - humoral immunity: B cells (B lymphocytes), which make antibodies
  - cell mediated immunity: T cells (T-lymphocytes)
- B and T cells comprise effector cells (cytotoxicity, antibody production, cytokine secretion, as applicable), regulatory cells and memory cells. Both are manufactured as needed from specialised stem cells.
- Each B cell and T cell expresses on its surface an antigen receptor that is different to all others, such that all possible invaders have their own, pre-existing, matching B and T cells ready to respond if and when required. B and T cells are triggered to respond by recognising a part of the pathogen through their antigen receptors.
- When memory B and T cells are reactivated by the same or a related pathogen, the adaptive immune response is much quicker and greater because the specific lymphocytes needed have already been manufactured.

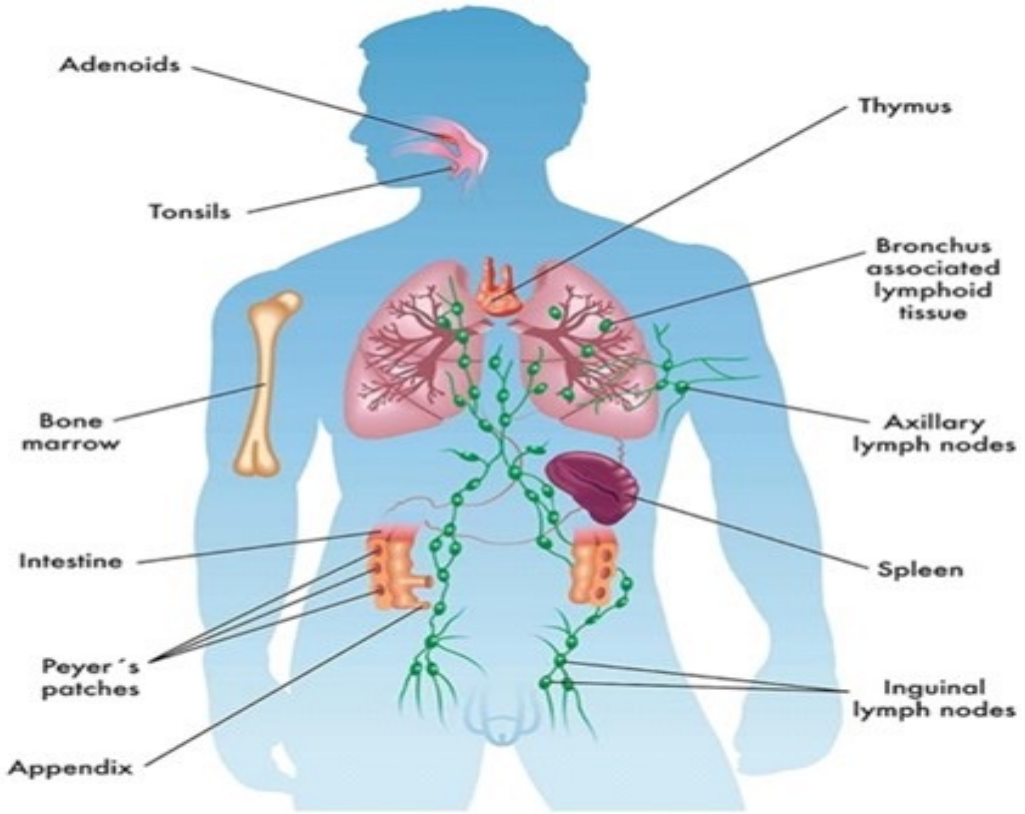
Life cycle of the B and T lymphocytes

- B and T lymphocytes are manufactured as needed from specialised stem cells in the bone marrow. B lymphocytes (B cells) take their name from the ‘B’ in ‘bone marrow’.
- They then circulate through the blood and tissues but generally congregate in lymphoid organs (see next slide), waiting to be activated.
- Once activated, B and T cells proliferate (clonal expansion) and differentiate according to function.
- Once the pathogen has been removed from the body, most of the B and T cells die off (around 90%) by apoptosis. Apoptosis is mediated via the mitochondria, allowing release of cytochrome c into the cytosol, which activates caspases.
- Similarly, the number of antibodies in circulation will reduce as they are bound to the pathogen, which will automatically reduce the adaptive immune response.
- Only the memory B and T cells will be left (around 10%), waiting to be reactivated by the specific antigen or antigen family. Their response is extremely rapid, mounting an attack so quickly that often no symptoms are experienced.



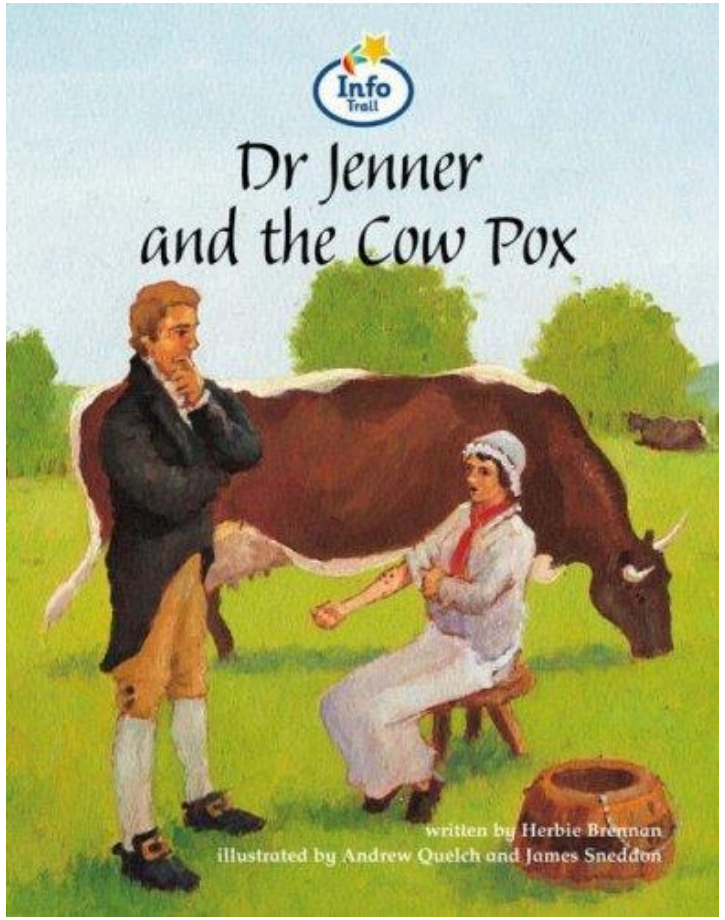
A scanning electron microscope image of a single human lymphocyte

Lymphoid organs



How the adaptive immune system was discovered

- In the 18th century, smallpox was a very serious, disfiguring and often fatal disease.
- Dr Edward Jenner observed that milkmaids often contracted cowpox, a relatively mild condition, with lesions similar to those of smallpox. He also observed that milkmaids who had contracted cowpox almost never caught smallpox and wondered if cowpox conferred some protection.
- He extracted some pus from the cowpox lesions and infected it into the blood of a small boy. He later injected the boy with pus from smallpox lesions. The boy did not contract smallpox.
- Jenner's experiment showed that if the immune system is given time to prepare, it can produce a defence against a micro-organism it has never seen before.
- This became the basis for classical vaccination (from 'vacca', a cow in Latin).



Humoral immunity: B Lymphocytes (B cells)

- B cells develop from haematopoietic stem cells (HSCs) that originate from bone marrow. They don't kill viruses themselves. Their main functions are to act as antigen-presenting cells (APCs), make antibodies and secrete messenger cytokines.
- Since most pathogens enter the body through the mucous membranes of the respiratory and gastrointestinal system, it is not surprising that the mucosal immune system comprises >50% of all lymphocytes. Mucosa-associated lymphoid tissue (MALT) is widespread in the body as, principally, gut-associated lymphoid tissue (GALT), BALT in the bronchi and so on.
- Some viruses, specifically Epstein-Barr (EBV) and human herpes virus 8 (HHV8) can inhibit the function of the B cell receptor to further their survival. Inhibition will not lead to B cell activation, clonal expansion or antibody production.
- B cells provide around 30 each of the 100 million specialised B cells required to produce all the different types of antibody we need for immune protection, hence clonal expansion/proliferation is necessary. This process lasts about a week and by then there will be around 20,000 clones of the original B cell, all with surface receptors which are specific for the antigen. The antigen-specific receptors then initiate further signalling pathway,s such as cytokine release.
- As well as producing antibodies, B cells have further roles as antigen-presenting cells (APCs) and cytokine secretors.

Principal B cell types in viral infection

- Naïve B cells: B cells not yet exposed to an antigen, circulating throughout the body in the lymphatic system. When they encounter an antigen through their surface antigen-specific receptors, they bind with it, triggering the maturation process, where they undergo clonal differentiation and proliferation into plasmablasts. They also initiate signalling pathways such as cytokine release.
- Plasmablasts: Short-lived, proliferating, antibody-secreting cells arising from B cell differentiation, which appear within days of the infection. Their antibodies tend to have a weaker affinity towards their target antigen compared to plasma cells. Plasmablasts then differentiate into mature long-lived plasma B cells (LLPCs).
- Plasma B cells (LLPCs): Plasma B cells are long-lived, non-proliferating, antibody-secreting cells derived from plasmablasts. Plasma cells are generated later in an infection and produce more antibodies than plasmablasts with a higher affinity towards their target antigen. One plasma cell working at full capacity can produce around 2,000 antibodies per second. Serological memory is partly maintained by the LLPCs that reside in the bone marrow and continue to secrete antibodies.
- Memory B cells (MBCs): MBCs circulate through the body and can be rapidly activated following reinfection to produce antibody-secreting plasmablasts or to initiate secondary germinal centres (GCs). This can occur if the amount of antibodies in circulation is insufficient to block the new infection or if infection is by a variant of the initial pathogen that has escaped recognition by the existing, highly specific antibodies. Memory B cells express the same antibody as the parent B cell.

B cell maturation

- Maturation of antigen-exposed naïve B cells may be T follicular helper (TFH) cell-dependent or T cell-independent (extrafollicular).
- T follicular helper (TFH) cells, a specialised subset of CD4+ T cells, provide help to B cells in germinal centres (GCs).
- GCs are transient microstructures formed within the follicles of secondary lymphoid tissues. Here TFH cells facilitate maturation of naïve B cells and their clonal differentiation and proliferation into plasmablasts to produce high-affinity neutralising antibodies.
- GCs also help establish a pool of specific memory B cells (MBCs), ready to respond rapidly to possible reinfection. MBCs circulate through the body or reside in the lymphoid organs and function as memory ‘stem cells’, which can quickly produce plasmablasts followed by LLPCs on reinfection.
- Whether the adaptive immune system carries out T cell-dependent or independent B cell maturation depends largely on the type of antigen.
- Extrafollicular (T cell independent) B cell activation does not generate germinal centres; although the B cell response is relatively rapid, antibodies generated (mostly IgM) tend to have lower affinity and are less functionally versatile than those generated from T cell-dependent activation.

Memory B cells (MBCs)

- The response of memory B cells is far greater and faster than that of naïve B cells for several reasons:
  - There are more of those that are specific to the antigen.
  - They differentiate into plasma cells more rapidly.
  - Whereas the initial response is from naïve B cells to produce IgM antibodies followed by IgG or IgA, memory B cells immediately produce IgG or IgA and continue to do so.
  - Because of the high frequency of somatic mutation in the immunoglobulin genes during B cell proliferation, a few B cells emerge whose antibody has a higher affinity for the antigen. As antigen levels decline, these B cells are preferentially selected for stimulation, so the affinity of the total antibody population increases, sometimes up to 100-fold.
- Memory B cells are particularly helpful where antibodies are insufficient for neutralising immunity or if the infection is by a variant of the initial pathogen that has escaped recognition by the existing, highly specific antibodies. MBCs can respond to variants because as a population, they possess a broader spectrum of affinity and reactivity than is present in antibodies. They can improve the response to counter the viral variant, producing fresh MBCs and plasma cells with improved specificity and affinity for the new variant.
- MBCs can be reactivated by interaction with memory CD4+ T cells, which secrete signalling cytokines. Memory T follicular helper (mTfH) cells function like MBCs in that their presence increases the likelihood and speed of secondary antibody responses.
- Although they cooperate, memory B cells and LLPCs are functionally different from each other: long-lived plasma cells mediate prompt and effective protection via pre-existing antibodies as the first line of defence, while MBCs serve as the backup of pre-existing antibodies by robustly supplying plasma cells in response to re-invading antigens. Plasma cells in the bone marrow decline from peak to baseline within 1 year. By contrast, memory B cells increase in numbers in 2–3 weeks and are stably maintained for years or decades and rapidly differentiate into antibody-secreting cells upon antigen re-encounter.

Atypical memory B cells (atMBCs)

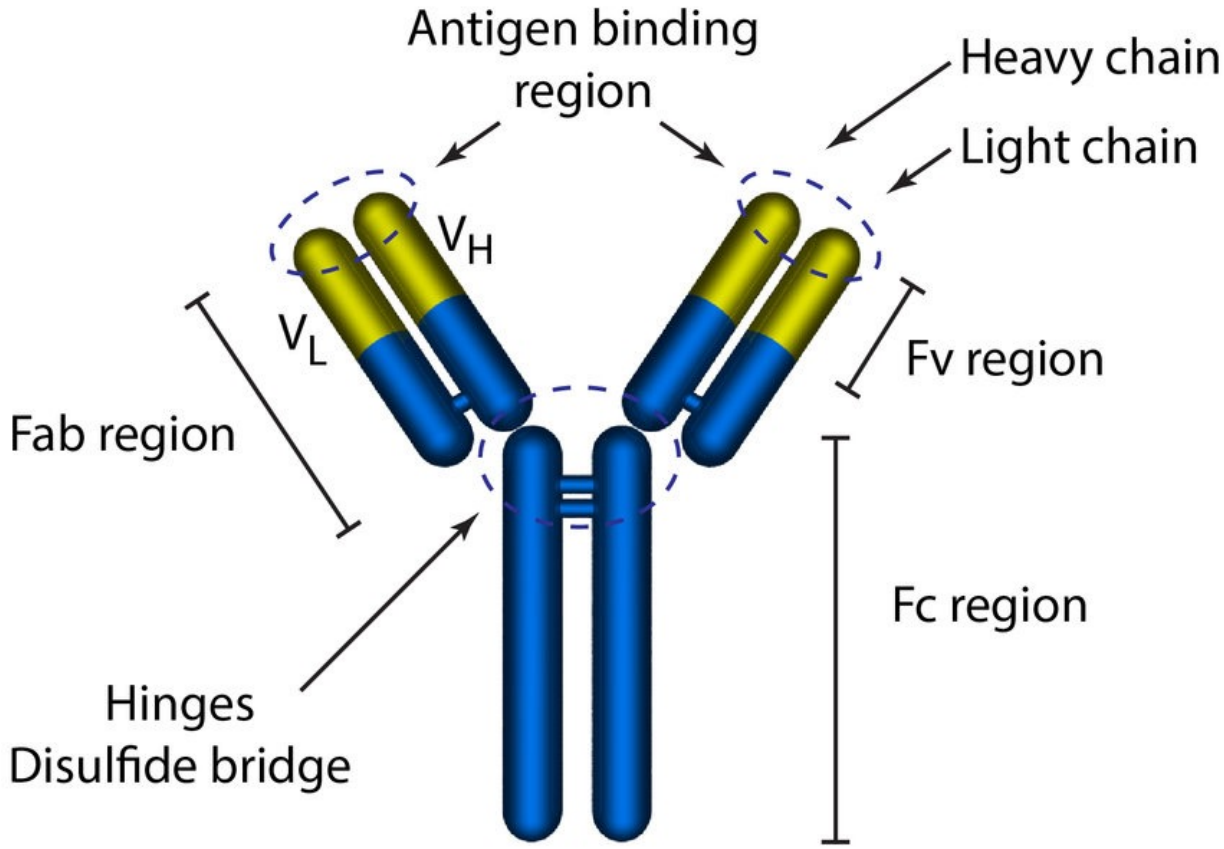
- In a healthy body, classical memory B cells (CD21+/CD27+) that recognise self-antigens are destroyed, so that they don't harm the body's healthy cells.
- However, it is known that atypical memory B-cells (atMBCs) can aberrantly appear during chronic infections, including HIV, malaria, HepB and HepC. Malignant transformation of B cells and their precursors can also cause a host of cancers.
- But if memory B cells are unable to recognise self-antigens as harmless, autoimmune disease can result from the antibody production. Autoimmune diseases where disease activity is correlated with memory B cell activity include scleroderma, multiple sclerosis, systemic lupus erythematosus, type 1 diabetes, post-infectious IBS and rheumatoid arthritis.
- The significance of atMBC production during viral infections and whether this may be associated with impaired B-cell function is still controversial, and it is unclear whether these cells are also functionally defective in COVID-19. (Oliviero B. Expansion of atypical memory B cells is a prominent feature of COVID-19. Cell Mol Immunol. 2020; 17:1101–1103)
- A 2015 study suggests that atypical B cell production may be due to hypomethylation (Kulis M, et al. Whole-genome fingerprint of the DNA methylome during human B cell differentiation. Nature Genetics. 2015; 47 (7): 746–756)

Antibodies (immunoglobulins - Ig)

- When we are infected with a virus, antibodies are produced against many epitopes on multiple virus proteins.
- Antibodies are glycoproteins, derived from B cells, that circulate in the bloodstream. They can quickly detect pathogens and then bind to them. An antibody only attaches to an antigen if it matches exactly, like a key in the lock of the antibody.
- Antibodies cannot enter a cell unless complexed with a virus.
- Antibodies have three main functions:
  - They neutralise pathogens (neutralising antibodies)
  - They activate other immune system cells by attaching to their surfaces (binding antibodies).
  - They activate proteins that help in the immune system response (neutralising and binding antibodies).
- Antibodies also support the innate immune system.
- Antibodies are highly specific, so antibodies to an H1N1 virus will not protect us against an H2N2 virus.
- There are around 1,000 genes for antibody production, yet through combinations they can produce up to 2.6 million different antibodies. When mutation is also taken into account, they can produce many billions.

Antibody structure

- Antibodies are made up of 4 polypeptide chains: 2 identical long (heavy) chains and 2 identical short (light) chains.
- This results in a Y-shaped molecule, with the variable regions at the 2 tips of the arms of the Y (Fab region).
- The stem (the Fc region) determines the class of antibody: IgA, IgG etc.



Antibody classes: Immunoglobulins (Ig)

- There are 5 antibody classes: IgA, IgD, IgE, IgG and IgM, all of which have different biological effects. The class is determined by the antibody Fc (fragment crystallisable) region.
  - IgM is found exclusively in the blood, where it is the largest protein. It can activate complement and can effectively immobilise and agglutinate microbes. IgM is the default antibody class and is the first antibody produced by B cells.
  - IgG is the most useful and constitutes around 75% of antibodies found in the blood but is also active in the tissues. It can activate both complement and phagocytosis and can cross the placenta to give the foetus the mother's immunity.
  - IgA functions at mucosal surfaces (e.g. gut and respiratory system) and has components to protect it from proteolysis. It constitutes about 2/3 of all antibodies found in the body (not just in the blood).
  - IgE is only present in trace amounts. It can trigger inflammation but is also the cause of allergies.
  - IgD is found on B cells, not in serum, and is part of their activation pathway.
- IgG and IgM protect against bacterial and viral infections and are commonly found in blood, although IgM production can be transient. IgA is mostly found in mucous membranes as well as blood and nasal secretions.
- IgA and IgG antibodies can persist for extended periods in blood and nasal fluids.

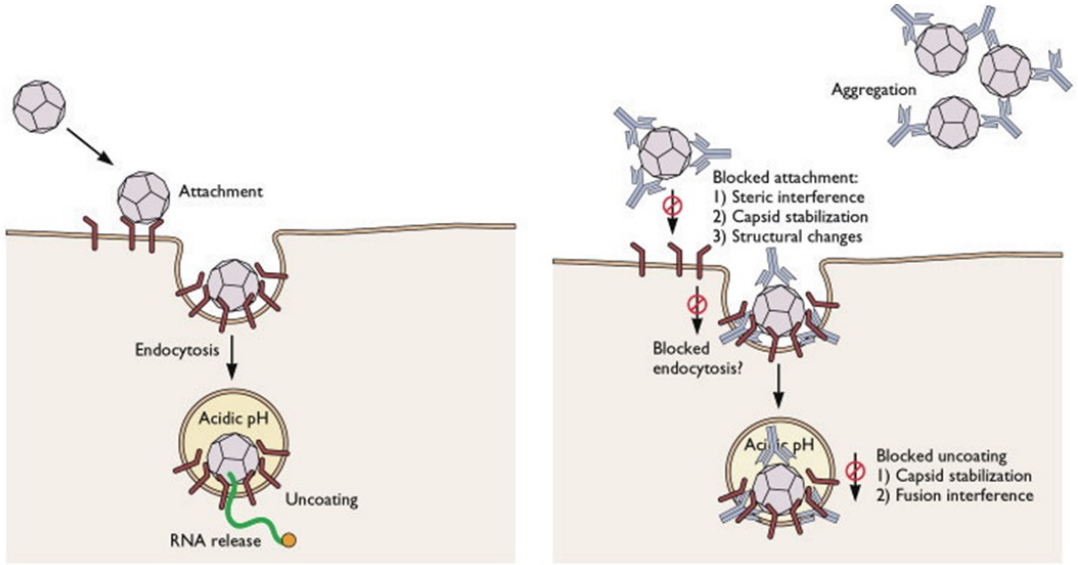
Binding and neutralising antibodies

Antibodies may be binding or neutralising.

- Binding antibodies bind to a virus. They do not destroy or neutralise it but they may
  - tag it for destruction by immune cells (macrophages, T cells and NK cells);
  - trigger viral agglutination (clumping together), making them an easier target for immune cells;
  - activate complement proteins, which enhance (opsonise) phagocytosis of viruses and damage the envelope (phospholipid bilayer) that is present on some types of virus, including SARS-CoV-2.
  - bind to Fc receptors of the surface of phagocytes to trigger phagocytosis (the phagocyte engulfs and 'eats' the virus).
- Neutralising antibodies neutralise the virus by directly attaching to the cell surfaces of the pathogen to prevent it binding to cell receptors and entering and thereby infecting the cell. Binding to the viral capsid can inhibit uncoating of the genome and block interaction with the cell receptor. Neutralising antibodies can also stop virions (viral particles) from changing their structure and shape, known as conformational change, in order to enter and replicate within a cell. By preventing entry to the cell, neutralisation reduces infectivity and replication.
- IgG, IgA and IgM antibodies can all be neutralising but for respiratory and gut viruses, IgA will be the key antibody for neutralisation.
- Once the virus has been neutralised it is degraded by white blood cells and excreted through urine or faeces.
- Neutralisation is thought to be the main mechanism of immune protection to most infections, although the pathogen may evade the antibodies to enter the host cell.

How antibodies neutralise or destroy a virus

- Neutralising antibodies can directly neutralise the virus, preventing it from entering a host cell. This will effectively destroy it, as viruses need host cells to thrive and replicate.
- Binding antibodies may tag the virus/antibody complex for destruction by phagocytes and other immune cells (the phagocyte engulfs and ‘eats’ the virus). The virus/antibody complex binds to Fc receptors on the surface of phagocytic cells to trigger phagocytosis.
- They can also activate complement proteins, which enhance phagocytosis of viruses (opsonisation) and damage the envelope (phospholipid bilayer) that is present on some types of virus.
- Antibodies can cause viruses to agglutinate (clump together), making them an easier target for immune cells than single viral particles.
- Antibodies may interfere with virion binding to receptors, block uptake into cells or prevent uncoating of the genomes in endosomes.



Racaniello V.
https://www.virology.ws/2009/07/24/virus-neutralization-by-antibodies/

Antibody-dependent enhancement (ADE)

- Some viruses are known to use antibody-dependent enhancement (ADE) to aid survival by using the host's antibodies inside the immune cell in order to destroy the cell.
- This is known as an immune evasion strategy, avoiding intracellular innate immune sensors or pattern recognition receptors.
- ADE has been identified in over 40 positive-strand RNA viruses, including Flaviviruses (such as Dengue virus), Yellow fever virus, Zika virus, Coronaviruses, Orthomyxoviruses (such as influenza), Retroviruses (such as HIV) and Orthopneumoviruses (such as RSV).
- ADE can also be known as immune enhancement, antibody-dependent cellular cytotoxicity, pathogenic priming and, when related to vaccines, vaccine-enhanced sensitivity (VEH), paradoxical immune enhancement or vaccine associated disease enhancement (VADE). The only term that is truly descriptive of this phenomenon is ‘pathogenic priming’.

Antibody-dependent enhancement (ADE): mechanisms

- In a healthy immune system where substantial amounts of antibodies have been produced and bound to the antigen, an inhibitory signal, known as antibody feedback, is generated as the antigen/antibody complex binds to the B cell receptor. But this doesn't always work!
- ADE can occur when a virus binds to non-neutralising (i.e. binding) antibodies which then assist the virus to enter cells rather than tagging it for destruction; it is not entirely clear if this can also occur with neutralizing antibodies. In ADE, the virus will normally be able to replicate once it has entered a host cell and may exacerbate disease via excess secretion of pro-inflammatory cytokines and increased complement deposition in the tissues. It has been described as acting as a 'Trojan horse'.
- ADE is mainly mediated by IgG antibodies, however, IgA and IgM together with complement have also been shown to trigger ADE.
- This can occur mainly through 2 known mechanisms, although in practice there may be more.
  - The antibodies can interact with receptors on immune cells (monocytes, macrophages and B cells), allowing the virus-antibody complex to be brought into the cell by endocytosis, thereby enhancing infectivity because the virus can now replicate.
  - The antibody Fc region, found in the tail region of the antibody, can interact with immune cells which display Fc receptors (FcRs) and complement receptors on the immune cell surface. The interaction forms an 'immune complex'.
- FcRs do have a beneficial function, which is to bind to antibodies to stimulate phagocytic or cytotoxic cells to destroy the antigen or infected cell containing the antigen.

Why is antibody-dependent enhancement (ADE) of concern?

- Antibody-dependent enhancement (ADE) has been associated with severe infection and disease outcomes in many viral infections, particularly with respiratory viruses.
- It has been suggested that ADE is one of the mechanisms causing hyperactivation of macrophages and monocytes, leading to the often fatal cytokine storm.
- Human coronaviruses normally enter cells through ADE with the assistance of the FcR. Both SARS-CoV-1 and MERS caused enhanced lung injury by inducing hyperimmunity through the interactions of antibodies and the FcR, which alter the functions of macrophages.
- Several experts have warned of the potential for ADE with antibody therapies and vaccines that trigger antibody production.
- For example, vaccinations against Dengue virus and a coronavirus affecting cats were deemed unsuccessful because they resulted in antibody-dependent enhancement that made the infection worse in those that had been vaccinated when compared to those that had not been vaccinated.

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Cell-mediated immunity: T lymphocytes (T cells)

- T cells are needed once the virus has penetrated a cell, since antibodies cannot enter cells unless complexed with the virus in ADE.
- Although T cells are manufactured from haematopoietic stem cells in the bone marrow, they mature in the thymus, which is why they are called ‘T cells’. Humans have roughly 1 trillion T cells.
- T cells are very similar to B cells in appearance but whereas B cells can quickly manufacture new specialised B cells (with the antibody as a surface receptor), it takes around a week to produce and multiply cloned specialised T cells (‘clonal expansion’) in a customised immune response. This is the reason for lymph node enlargement during infection.
- T cells express CD4+ or CD8+ receptors, but not both. CD4+ and CD8+ receptors are glycoproteins found on the surface of T cells (see later slide).
- T cell action is usually short range and transient and consequently T cells have to travel to the site of the antigen, often the point of entry into the tissues such as the airway epithelium. The migration of T cells is promoted by inflammatory chemokines and increased expression of adhesion molecules on the vascular endothelium at the site of infection.

T cell types and functions

- Killer T cells: CD8+ cytotoxic T lymphocytes (CTLs), of which the human body has roughly a trillion. They are able to destroy only those pathogens which have been tagged by other immune molecules (antigen presentation – see next slide).
- T helper (Th) cells: CD4+ T helper cells aid the activity of other immune cells by releasing cytokines and stimulating faster expansion of CTLs to hasten pathogen clearance from the body.
- T follicular helper cells (TFH) cells: a specialized subset of CD4+ T cells, which aid B cells in germinal centre production.
- Regulatory T cells (Tregs): CD4+ regulatory T cells are the adaptive immune system's 'off switch' to promote immune tolerance and prevent autoimmunity.
- Memory T cells: Memory T cells 'remember' the biochemical signature of the specific antigen involved in each encounter. Should this antigen enter the body again it would be recognised by memory T cells and a rapid and specific immune response would be mounted. Memory T cells may derive from CD4 helper or CD8 cytotoxic T cells. Memory T cells may also comprise tissue resident memory (TRM) T cells and stem cell-like memory T (TSCM) cells.

What are CD4 and CD8?

- To ensure that the right type of T cell is applied to the target cell, T cells also have Cluster of Differentiation (CD) surface molecules. These are single molecules or groups of molecules on the surface of a cell that is highly specific to that cell, allowing it to be identified amongst others.
- The CD molecules often act as ligands or receptors, though may also have some unrelated function such as cell adhesion, and may consist of a mixture of proteins, glycoproteins and glycolipids. Some are trans-membrane, while others are entirely extracellular.
- CD4 and CD8 are glycoproteins found on the surface of immune cells (T helper cells and cytotoxic lymphocytes, respectively).
- Cells expressing MHC Class I (see next slide) are normally the cells containing the virus and need cytotoxic CD8 T cells, while cells expressing MHC Class II are normally B cells, macrophages and dendritic cells which need CD4 helper T cells.
- This ensures that CD4 helper T cells are not sent in to kill the virus, as they would not achieve their aim!

Antigen presentation by APCs and MHCs

- Unlike antibodies, which bind to antigens directly, T cell receptors can only recognise antigens that are bound to certain receptor molecules, known as Major Histocompatibility Complex (MHC). These MHCs are membrane-bound surface receptors on antigen presenting cells (APCs), such as dendritic cells and macrophages.
- The presence of the virus has already triggered interferon release by the innate immune system. Interferons upregulate expression of MHCs.
- On contact, MHCs convert the antigen by means of proteases into small peptides, known as epitopes, within the APC. The epitope is then displayed on the surface of the infected cell for display to T cells.
- The APCs are then transported to lymphoid organs, where the MHC molecules on the cell surface advertise the presence of the virus-infected cell using the epitope.
- On presentation of the epitope to the T cells, they bind to the antigen epitope, which triggers clonal differentiation and expansion of the appropriate specialised T cell, as well as production of cytokines.
- When sufficient T cells have been manufactured, they will then mature into effector T cells, and be released into the circulation to do their job.

More on MHCs

- MHCs may be Class I or Class II. Class I MHCs are expressed by most cells in the body, while Class II MHCs are only expressed on immune system cells and inform helper T cells on what is occurring outside the infected host cell.
- In humans, MHCs may also be known as human leukocyte antigen (HLA). It is MHC molecules that are tissue typed for compatibility between transplant donors and recipients.
- It is thought that individuals do not have identical MHCs in order that we are not all susceptible to the same infection, which might then wipe out the entire human race. But differences in MHC type are certainly responsible for individual differences in response to the same infection.
- When the T cell is developing in the thymus, it is presented with self-MHCs and self-peptides, so that it learns to distinguish self from invading microbe.

T cell antigen presentation

- T cells specialise in recognising protein antigens but the antigens must be properly presented by an antigen presenting cell before the T cell recognises the antigen.
- They need a formal introduction!
- This is carried out by antigen presenting cells (APCs) and major histocompatibility complexes (MHCs) within the APCs.
- APCs may be activated macrophages, dendritic cells or B cells (all white blood cells).

Killer T cells (Cytotoxic T lymphocytes – CTLs)

- Cytotoxic T lymphocytes (CTLs) are specialised to recognise viral epitopes (peptides bound to MHC Class I antigens) and will then destroy all cells around them expressing this epitope.
- The massive expansion of antigen-specific CD8 T cells that occurs in response to viral infection is critically dependent on the direct action of type I interferons on CD8 T cells.
- CTLs kill via 3 mechanisms:
  - Apoptosis via caspase activation: Perforins penetrate the host cell membrane and granzymes (granule-derived enzymes) activate caspases in the host cell cytosol to induce cellular apoptosis. Granzyme B is the principal enzyme employed.
  - Apoptosis via host cell Fas surface molecules (aka the 'death receptors'), which interact with CTLs via the Fas ligand to trigger apoptosis.
  - Secretion of proinflammatory cytokines (principally IFNγ).
- CTLs are 'serial killers', in contrast to antibodies. Once the host cell, and hence the virus inside the cell, has been destroyed, the CTL disengages and searches out another virus-infected cell.

T helper (Th) cells

- Upon acute viral infection, virus-specific CD4+ T cells differentiate into either helper T cells or T follicular helper (TFH) cells.
- CD4+ T helper (Th) cells are cytokine factories, all secreting IL-2 on activation. Once proliferation has occurred, other cytokines are secreted which are specific to the Th type:
  - Th1 cells principally secrete IL-2, IFNγ and tumour necrosis factor (TNF) to activate antibodies and elements of the innate immune system. We are most concerned with Th1 cells to combat viruses.
  - Th2 cells principally secrete IL-4, IL-5 and IL-13 to trigger B cells to proliferate and secrete antibodies and to stimulate production of other immune cells, principally polymorphonuclear leukocytes (PMNs), including neutrophils, eosinophils, basophils and mast cells, as well as haematopoietic cells in bone marrow to produce more T lymphocytes. They also promote IgE production by B cells.
  - Th1 cells inhibit the activation of Th2 cells and vice versa.
  - Th17 cells principally secrete IL-17 to recruit neutrophil production. Th17 is principally active against pathogenic bacteria and fungi but may also mediate allergic and autoimmune responses.
- Th1 cytokines, of which IFNγ is the most important, activate macrophages to kill the virus by further release of pro-inflammatory cytokines and chemokines, increased expression of MHC Class II and co-stimulators for further T cell activation. They also promote improved killing of the pathogen via increased reactive oxygen species (ROS) and nitric oxide (NO) via the induction of nitric oxide synthase (NOS).

T follicular Helper (TfH) cells

- TfH cells play a critical role in protective immunity helping B cells produce antibodies against foreign pathogens. TfH cells are located in secondary lymphoid organs (SLOs), which contain numerous lymphocytes, separated into defined T and B cell zones. Uniquely, TfH cells are found in the B cell zone and spend the majority of their time in close interactions with B cells.
- TfH cells play an essential role in the formation of germinal centres (GCs), which are distinct structures that form within the B cell zones of SLOs during an ongoing immune response. B cells within GCs undergo rapid proliferation and antibody diversification, allowing the production of many types of antibody, with greater affinity for their targets. GCs are also the site where B cells can differentiate into antibody secreting plasma cells and memory B cells which allow long lasting antibody production. Cytokine production by TfH cells determines the type of antibody produced. In the absence of TfH cells, GCs do not form.
- TfH cell function is dysregulated in a number of diseases of excessive antibody production, such as autoimmune conditions, and in patients with immunodeficiency.
- Virus-specific TfH cells differentiate into memory cells, protecting against re-infection by the same viruses by providing immediate help to virus-specific memory B cells.

Regulatory T cells (Tregs)

- CD4 regulatory T cells (Tregs) used to be known as ‘suppressor T cells’.
- They modulate the immune system, maintain tolerance to self-antigens and prevent autoimmune disease. To facilitate this, they secrete the soluble messengers IL-10, TGFβ and adenosine, which suppress the activation, proliferation and cytokine production of CD4+ T cells and CD8+ T cells. They may also suppress B cells and dendritic cells.
- As well as the CD4 T cell co-receptor, they may also express CD25, which is a component of the IL-2 receptor. Tregs are thus CD4+ CD25+.
- They also express the nuclear transcription factor Forkhead box P3 (FoxP3), which determines Treg development and function and is crucial for maintaining suppression of the immune system. FoxP3 primarily acts against self-antigens to prevent autoimmunity.

More on immune tolerance and Tregs

- Some of these Tregs, which protect against allergy and autoimmunity, only emerge after contact with the parasites, bacteria, viruses and fungi of the outside world.
- The prevalence of allergy and autoimmunity is increasing rapidly. Estimates are that up to 20% of the US population now suffers from an autoimmune condition.
- Scientists have observed that autoimmunity rates are highest in societies with the least amount of contact with microbes and parasites. This lends support to the 'hygiene hypothesis', which states that early childhood exposure to microorganisms protects against allergic diseases by contributing to the development of the immune system and prevents defects in the establishment of immune tolerance.
- A 2016 UK study from the Royal Society for Public Health showed that our interaction with external microbes and the human microbiome plays an essential role in immune regulation. The authors highlighted the importance of increased social exposure, less time spent indoors and diet, all of which may help restore the microbiome and reduce risks of loss of immune tolerance. (Bloomfield SF, et al. Time to abandon the hygiene hypothesis: new perspectives on allergic disease, the human microbiome, infectious disease prevention and the role of targeted hygiene. Perspectives in Public Health. 2016;136(4):213-224)

Memory T cells

- Memory T cells derive from CD8+ cytotoxic T cells or CD4+ helper T cells. They may take several forms:
  - Effector memory T cells, which are located in the tissues and retain the properties of the original T cells,
  - Central memory T cells, which are located in lymphoid organs and behave like undifferentiated T cells.
  - Tissue resident memory (TRM) T cells
  - Stem cell-like memory (TSCM) T cells
- Memory T cells can be activated by the same pathogen, a pathogen that shares antigens with the original pathogen (i.e. it is cross-reactive or heterologous) or by high local levels of cytokines induced by unrelated pathogens (bystander effect).
- Memory T cells can persist for many years. Even if a virus mutates, its waste products that are recognised by the CTLs remain very similar and will still be destroyed.
- Immunological memory is a mechanism to protect us against reinfection. However, having immune memory to a pathogen does not necessarily mean having immunity to reinfection; sometimes, immune responses are directed at irrelevant targets on the pathogen or the protective components of the immune memory can diminish to a point of non-functionality.

Tissue resident memory (TRM) T cells

- Tissue resident memory (TRM) T cells are specialised T cell populations that reside within tissue sites and are able to respond relatively fast upon reinfection, because they are already present at the location of viral entry.
- TRM T cells are distinct from circulating memory cells, including central and effector memory T cells, both functionally and transcriptionally.
- CD4+ TRM protection is mediated by IFN-γ, as well as early induction of both innate and virus-specific CD8+ T cell responses.
- CD4+ and CD8+ TRM T cells are abundant in most tissues, however, TRM T cells will most likely not be detected in blood, thereby giving a false impression that memory T cells are absent in the individual.
- CD4+ TRM T cells have been found to contribute both to protective and pathogenic roles in disease as they can polarise into a multitude of distinct subsets and recognise not only viruses and intracellular bacteria but also extracellular bacteria, fungi, and parasites. CD4+ TRM T cells have been implicated in various pathologies.

Stem cell-like memory (TSCM) T cells

- Stem cell-like memory (TSCM) T cells are a rare subset of memory lymphocytes endowed with the stem cell-like ability to self-renew and the multipotent capacity to reconstitute the entire spectrum of memory and effector T cell subsets.
- The success of long-term memory T cells depends on the generation of stem cell-like memory (TSCM) T cells since they have a higher self-renewal ability.

T cell exhaustion

- T cell exhaustion appears to be the main mechanism underlying immune dysfunction during chronic viral infection, It occurs when chronic antigen stimulation causes cytotoxic T lymphocytes (CTLs) and T helper cells to become dysfunctional, with depleted proliferative capacity. They also produce much lower amounts of pro-inflammatory cytokines (IL-2, IFNγ, TNFα and others) and are unable to kill virus-infected cells or cancerous tumours or develop memory T cells. The resultant incomplete immune response drives the spread of the pathogen or cancer; the phenomenon also is seen in autoimmunity.
- Exhausted T cells appear to remain programmed to stay exhausted even many weeks after exposure to a virus ended and may then die off by apoptosis without regaining normal function; those that do survive tend to be memory T cells and may show only partial recovery.
- Exhausted T cells also display a distinct metabolic phenotype, with reduced glucose uptake as well as mitochondrial dysfunction, which reduces capacity for oxidative metabolism.
- Over-activated and exhausted T cells can start over-expressing certain inhibitory markers, such as the immune checkpoint protein, programmed cell death 1 (PD-1), a membrane glycoprotein receptor involved in establishing tolerance.
- The precise mechanisms controlling the development of T cells into an exhausted state are still poorly understood. One suggestion is that activation of inhibitory markers is a mechanism to prevent over-stimulated CTLs from attacking host tissue rather than infected cells in autoimmune and other conditions; curiously their presence is associated with better prognosis of immune-mediated inflammatory diseases.

Unconventional T cells: Gamma delta (γδ) T cells

- Most T cells are alpha beta (αβ) T cells with a T cell receptor (TCR) composed of two glycoprotein chains, α and β. In contrast, gamma delta (γδ) T cells have a TCR that is made up of one γ chain and one δ chain. They belong to a family known as 'unconventional T cells', which also includes mucosal-associated invariant T (MAIT) cells, which display features of both the innate and adaptive immune systems.
- This group of T cells is usually less common than αβ T cells, but are at their highest abundance in the mucosa, within a population of lymphocytes known as intraepithelial lymphocytes (IELs).
- The antigenic molecules that activate γδ T cells are still largely unknown, as are the conditions that lead to responses of γδ T cells, although as part of the innate immune system they are known to respond to inflammation and stressed or infected cells. They have been observed acting as virus detectors, as phagocytes, as regulatory cells and as a bridge between the innate and adaptive immune system but it is clear that they have other important properties. They are considered a component of adaptive immunity in that they can affect TCR genes and can develop memory.
- γδ T cells secrete the usual T cell cytokines and chemokines, as well as cytotoxic components (perforin, granzymes) and interact with epithelial cells, monocytes, dendritic cells, neutrophils, and B cells. Some sub-types may also serve as antigen presenting cells.
- However, γδ T cells do not seem to require antigen processing and major-histocompatibility-complex (MHC) presentation of peptide epitopes, although some recognize MHC class I molecules.
- γδ T cells are also believed to have a prominent role in recognition of lipid antigens. They are of an invariant nature and may be triggered by alarm signals, such as heat shock proteins (HSP).

Mucosal-associated invariant T (MAIT) cells

- Mucosal-associated invariant T (MAIT) cells make up a subset of T cells in the immune system that display effector-like qualities. They are capable of recognizing bacterial and fungal ligands derived from vitamin B biosynthesis.
- Although only relatively recently discovered, they are abundant in humans, where they are found in the blood, liver, lungs, and particularly in the mucosa, defending against microbial activity and infection.
- Although T cells, they act as part of the innate immune system, secreting pro-inflammatory cytokines.
- They also support the adaptive immune response, can possess antigen memory and participate in tissue repair.
- MAIT cells are thought to play a role in autoimmune diseases, such as multiple sclerosis, arthritis and inflammatory bowel disease.

(Klenerman P, et al. Biological functions of MAIT cells in tissues. Mol Immunol. 2021 Feb;130:154-158)

The ‘Bystander Effect’

- More commonly associated with the effects of radiation, the bystander effect with respect to T cells is the activation of T cells independent of an antigen acting on a T cell receptor (TCR).
- It can be initiated by microbial sensors such as cytokines, Toll-like receptors (TLRs), superantigens, molecular mimicry and dual T cell receptor signalling. Specifically, IL-12, IL-15 and IL-18 can boost bystander T cell responses during microbial infection.
- The threshold for T cell activation is often lowered due to a dysregulated inflammatory environment during infection, providing an opportunity for T cell signalling to occur outside of the stringent and conventional TCR-triggering pathway. Pathogen recognition by innate receptors on T cells can deliver unconventional co-stimulatory signals which subsequently influence disease outcome.
- Antigen-independent activation often results in the secretion of pro-inflammatory molecules such as IFNγ and granzyme B, which act in conjunction to perpetuate inflammation.
- Nevertheless, generally the bystander effect is believed to be beneficial to host defence.

(Whiteside SK, et al. Bystander T Cells: A Balancing Act of Friends and Foes. Trends Immunol. 2018 Dec;39(12):1021-1035)

Components of both the innate and adaptive immune systems: Natural killer (NK) cells

- Natural killer (NK) cells are innate lymphoid cells (ILCs), lymphocytes in the same family as T and B cells and are part of both the innate and adaptive immune systems. NK cells are activated principally by interferons.
- NK cells are descended from haematopoetic stem cells and mature in the bone marrow. Once activated and sent to the point of infection, they proliferate rapidly. They are short-lived, with a half-life of about a week, and reside in the blood, liver and spleen.
- Unlike killer T cells, NK cells have no receptor so cannot recognise a virus from the MHC on an APC; in fact they specialise in destroying cells that have a reduced number of MHC class I molecules on their surface. Instead, they recognise a signal from secretion of peptides at the surface of the infected cell.
- They can destroy the virus before it enters a cell (innate immune response) and they can destroy cells infected with a virus by unleashing perforin, granzymes and pro-inflammatory cytokines to trigger apoptosis (adaptive immune response).
- This action is enhanced by cellular release of IFN-γ and TNF-α. Interferons prevent replication of viruses by directly interfering with their ability to replicate within an infected cell. They also act as signalling molecules which induce neighbouring cells to increase the numbers of MHC class I molecules upon their surfaces, giving greater warning of viral presence.
- NK cells are very useful in viral infections where the virus employs immune escape mechanisms such as turning off expression of the MHCs, thereby avoiding attack from the killer T cells. Since NK cells can’t recognise MHCs, they will attack the infected cell anyway.

Components of both the innate and adaptive immune systems: Inflammation and cytokines

- Pro-inflammatory cytokine activation is a vital part of the immune response to any pathogen, although excessive or inappropriate inflammation may become part of the problem. In many infections, it is the immune system that causes much of the pathology as the damage to host tissues will itself induce further pro-inflammatory cytokine release.
- If not controlled, this can lead on to the cytokine storm (known as cytokine release syndrome - CRS), acute respiratory distress syndrome (ARDS), septic shock, multiple organ failure and death.
- Anti-inflammatory cytokines should turn off the inflammatory response when no longer required but it is a delicate balancing act, allowing enough inflammation to kill the virus but not so much that death results.
- So every immune response against pathogens carries with it an incremental increase in inflammatory cytokine activation; the stronger the immune response, the greater the potential damage to host tissues, with the release of pro-inflammatory cytokines feeding greater cytokine release as a response to tissue damage. At this point, therapy has to shift from immune support to downregulation of the excessive inflammatory response. It is a delicate balancing act, allowing enough inflammation to kill the virus but not so much that death results.
- Over-consumption of a Western diet and sedentary lifestyles have produced populations with chronic metabolic inflammation, termed metaflammation. This contributes to many of today's chronic diseases (heart disease, obesity, type 2 diabetes etc). These are typically the diseases which are the risk factors for more severe COVID-19.
- If the immune system is preoccupied with producing metabolic inflammation, it has fewer resources to spare to protect against viruses, so we don't want to start off in an inflammatory state!

Interaction of the innate and humeral and cellular adaptive immune systems

- There is considerable B cell and T cell interaction: for example, B cells activate T cells to become helper T cells that then assist the B cell. The various cells of the adaptive immune system communicate either directly or via soluble chemical messengers such as cytokines.
- Almost all neutralizing antibody responses, duration of antibody responses, and affinity-matured B cell memory depend on CD4+ T cell help.
- Innate immune cells play an important role in processing and presenting antigens to B and T cells to induce antigen-specific immunity. In turn, these innate cells themselves respond to the activated B and T cells, as part of their antiviral immune response. Antibodies made by B cells can help the innate immune cells to recognise antigen.
- If innate defence mechanisms are sufficient to hold an infection at bay, then an adaptive immune response will likely not be triggered, and as a result, lasting immunity may not be achieved.
- [Maybe, then it would be better to catch any virus]

(Quast I. B cell memory: understanding COVID-19. Immunity. 2021; 54: 205; Vabret M. Immunology of COVID-19: Current State of the Science. Immunity. 2020; 52: 910)

How pathogens escape adaptive immunity

- Viruses inhibit MHC Class I expression which interferes with their production, transport to the cell surface and maintenance on the cell surface. This renders CTLs ineffective.
- They may prevent the host cell being killed by CTLs by inhibiting caspases and other mechanisms of apoptosis.
- They may inhibit cytokine release.
- Pathogens can cause immunosuppression, which with HIV is serious and long-lasting, with a steady loss of CD4+ (helper) T cells.
- Pathogen production of anti-inflammatory and immunosuppressive cytokines (e.g. IL-10).
- Production of decoy antigens, which attract the immune system away from the pathogen.
- Molecular mimicry: host-derived molecules taken up by the pathogen or pathogen mimicry of host antigens persuade the immune system that the virus is ‘self’.
- Continuously changing the shape (by mutation: antigenic drift) of important surface antigens to prevent the innate immune response progressing to a more effective adaptive immune response. This is one way the influenza virus evades neutralising antibodies.
- Pathogen-induced activation of polyclonal lymphocytes, which are not sufficiently specific to attack the pathogen and may restrict the host’s ability to mount an effective immune response, while inducing anti-self responses, potentially leading to autoimmune disease.

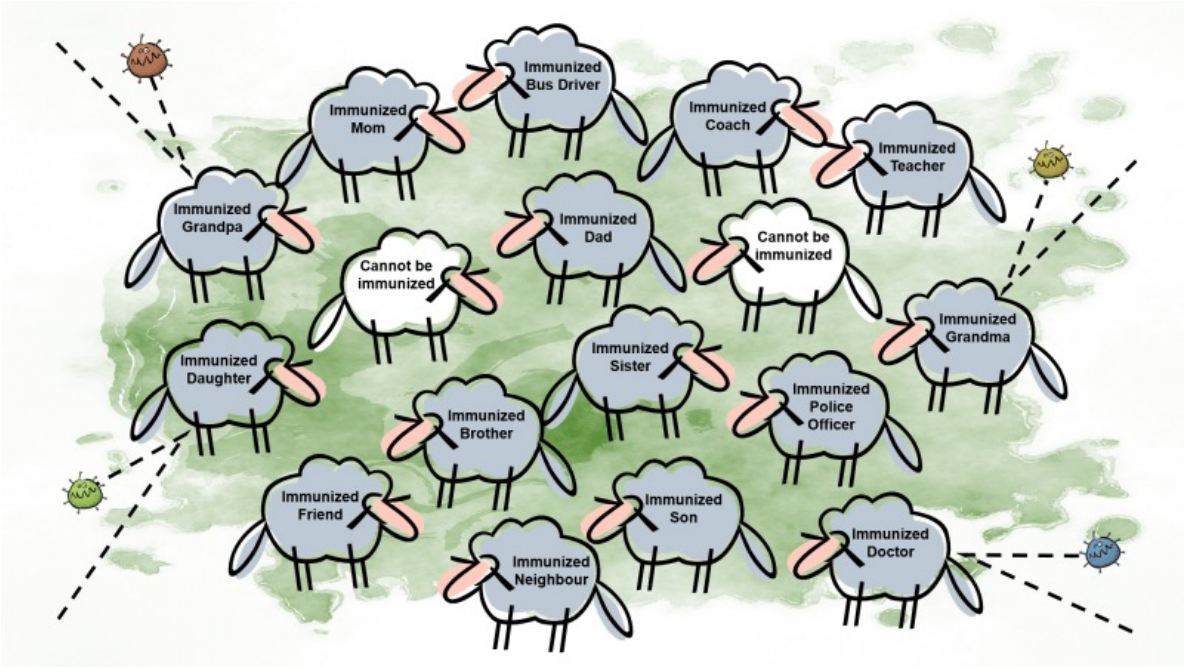
What can weaken the immune system

- Lack of exercise
- Lack of sunlight and low vitamin D
- Smoking
- Air pollution, including smoking and vaping
- Lack of immune challenge i.e. not exposing oneself to pathogens which trigger an immune response (‘Use it or lose it’!)
- Ageing (but not necessarily!)
- Lack of sleep
- Stress
- Anxiety/fear/stress
- Poor diet
- Obesity and other inflammatory disorders
- Excess alcohol

Immune function in ageing

- Immune function declines with age, a condition known as immune senescence, which includes loss of T and NK cells. Senescent cells are no longer able to divide; instead they build up in body tissue and secrete inflammatory cytokines that trigger inflammation and dysfunction. This much weaker and less complete immune response co-exists with overactivity of parts of the immune response, including autoimmunity.
- An early immune response is the most effective and this is one of the differences between a young immune system and a senescent immune system, where the innate immune response may be delayed.
- Ageing also increases systemic inflammation, known as ‘inflammaging’, defined as chronic low-grade inflammation occurring in the absence of overt infection.
- A low-grade inflammatory response may be the result of several mechanisms, including a compromised gut microbiome and obesity. As the body ages, it also slowly loses the ability to clear dead and dying cells, which subsequently increases inflammatory activity, in a vicious cycle.
- In the elderly the immune response to both infection and vaccination is known to be impaired.
- Senescent cells may also be involved in increased blood clotting, putting patients at greater risk of heart attack, stroke and venous thromboembolism, despite receiving prophylactic anti-clotting medication.
- Senescent cells also drive tissue fibrosis. This is seen particularly in the lungs, with fewer functional alveoli and progressive loss of the ability to inhale and exhale deeply to compensate to compensate. This gives rise to diseases such as chronic obstructive pulmonary disease, lung cancer and idiopathic pulmonary fibrosis, exacerbating the risk of respiratory viruses.

Herd immunity – or should that be ‘flock immunity’?



- Herd immunity occurs when enough people acquire immunity to an infectious disease such that it can no longer spread widely in the community. As a result, the whole community becomes protected — not just those who are immune.
- Herd immunity can be achieved by infection, vaccination or passive transfer (injection of serum or convalescent antibodies or maternal antibodies transferred across the placenta or in colostrum.
- There are huge uncertainties with all these methods.
- Herd immunity is not an exact science, as an individual’s susceptibility to infection varies depending on many factors, including their health, age, contacts within a community, immune system status etc.

Herd Immunity: definitions

- It is calculated using the reproductive number (R0), which is the estimated number of new infections that may occur from one infected person.
- R(0) = 1 means that one person who is infected is expected to infect one other person. If R(0) is <1 this indicates that cases are declining, while R(0) >1 suggests cases increasing.
- The herd immunity threshold (HIT) is the proportion of a population that needs to be immune for herd immunity to occur.
- It is calculated with the equation: HIT = 1 - 1/R(0), i.e. the more people who become infected by each infected individual, the higher the proportion of the population that needs to be immune to reach herd immunity.
- However, the HIT varies from disease to disease; the more contagious a disease is, the greater the proportion of the population that needs to be immune to the disease to stop its spread.
- Herd immunity does not mean that the virus has completely disappeared, only that it can no longer infect a critical mass of people and become an epidemic again.

Problems with the herd immunity concept

- The R0 assumes that everyone is susceptible to the virus, but that changes as the epidemic proceeds, because some people become infected and gain immunity. For that reason, a variation of R0 called the R effective (abbreviated Rt or Re) is sometimes used in these calculations, because it takes into consideration changes in susceptibility in the population. Furthermore, individuals with medical conditions, such as an immunodeficiency or immunosuppression, are unlikely to become immune.
- Pre-existing immunity and antigen mutation are ignored.
- In reality, populations are better described as social networks as individuals tend to cluster together, so that the HIT is more likely to be accurate for a social network than the population as a whole.
- The concept assumes that there are no interventions or behavioural change. In reality, people faced with a viral outbreak are highly likely to change their behaviour.
- A country's 'herd immunity' is often based on the results of antibody tests, as it is commonly believed that the only people who may have become immune to COVID-19 are those who show antibodies. This is a misconception, as we have seen that T cell immunity is longer lasting and may be more reliable.
- The HIT will never remain constant during a disease but can vary widely. Furthermore, a single pathogen will have multiple R0 values depending on the characteristics and transmission dynamics of the population experiencing the outbreak. This implies that the herd immunity threshold will vary between populations, which is a well-documented occurrence.
- In some people, the virus becomes blocked in the mucous membranes and never actually infects the cells, so an immune response is not mounted.
- The phenomenon of herd immunity doesn't actually confer immunity to the virus on individuals — it only reduces the risk that people will come into contact with the pathogen.

(Fine P, ''Herd Immunity'': A Rough Guide. Clinical Infectious Diseases 2011;52(7):911–916; Randoph HE, Herd Immunity: Understanding COVID-19, Immunity, 2020; 52: 737-741; https://www.nature.com/articles/d41586-020-02948-4; https://www.mayoclinic.org/diseases-conditions/coronavirus/in-depth/herd-immunity-and-coronavirus/art-20486808; https://www.nature.com/articles/d41586-020-02948-4)